

downregulation of the gene. The Examiner stated that if the expression of the gene is lower (in) colon cancer and polyps versus normal tissues the ratio of Cy5 to Cy3 should be less than one in cases of colon cancer or polyps. A value of 1 would be zero in the log base 2 scale, and values of less than 1 would be (a) negative number in the log base 2 scale. The Examiner stated that an examination of the log base 2 values shows numbers ranging from -3.64, -3.12, -1.92, +0.14, +0.52, and +1.04 for polyps and numbers ranging from -3.06, -2.73, -0.53, -2.86, -2.18, -1.99, -0.54, +1.1 and +1.29 for colon tumors. The Examiner then converted these values to log base 10 and concluded that:

"As these values range from 0.081 to 2.05 for polyp tissue and 0.119 to 2.44, it is not clear how one of skill in the art can make a diagnosis fo a colon disorder given the ratios presented in the Table. The indicated ranges imply that most of the Cy5/Cy3 ratios will be close to "1.0" which results from dividing by the normal value. Given a result of "1.0" one skilled in the art would not be able to make a diagnosis, as this value is the value attributed to normal tissue---".

Applicants submit that while the Examiner is correct in her interpretation of the log₂ values in column 1 of Table 1, the Examiner appears to be confusing absolute values with "log" values in converting the log₂ values to absolute values. The table below provides a direct comparison of the log₂ DE Cy5/Cy3 values for column 1 of Table 1 with their corresponding absolute values grouped, as the Examiner has done above, for colon polyp and colon cancer samples. The third column then shows the inverse of the absolute values for Cy5/Cy3 where the log₂ values were negative, i.e., where the ratio of the normal (Cy3) sample/ diseased (Cy5) sample was greater than 1. This value reflects the fold decrease of gene expression in diseased colon as claimed.

<u>Polyps</u>			<u>Cancer</u>		
<u>Log2</u>	<u>Absolute</u>	<u>Cy3/Cy5</u>	<u>log2</u>	<u>Absolute</u>	<u>Cy3/Cy5</u>
-3.64	0.0802	12.20	-3.06	0.1199	8.34
-3.12	0.1150	8.69	-2.73	0.1507	6.63
-1.92	0.2642	3.78	-0.56	0.6784	1.47
+0.14	1.10		-2.86	0.1377	7.26
+0.52	1.43		-2.18	0.2207	4.53
+1.04	2.05		-1.99	0.2517	3.97
			-0.54	0.6882	1.45
			+1.1	2.14	
			+1.29	2.44	

It is clear that 8 of the 15 values from either colon polyp or colon tumor samples showed significant downregulation (negative values) ranging from 3.78 fold to 12.20 fold. With downregulation values ranging from 4 to 12-fold in a majority of the samples (8/15) the Examiner's conclusion that "the indicated ranges imply that most of the Cy5/Cy3 ratios will be close to "1.0" is clearly incorrect. The data therefore supports the disclosure in the specification at p. 10, lines 14-16 that "Differential expression was considered significant if observed to be at least 2.5-fold in at least one patient and at least 2-fold in a majority of patients" and therefore more than adequately supports the use of the claimed polynucleotide in the diagnosis of colon cancer or colon polyps. Withdrawal of the rejection of claims 1-13 under 35 U.S.C. § 101 for lack of utility and likewise for lack of enablement under 35 U.S.C. § 112, first paragraph, is therefore requested.

The Examiner stated that all other rejections and objections as stated in Paper No. 9 are withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. 09-0108, as set forth in the enclosed fee transmittal letter.

Respectfully submitted,

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